BJA

British Journal of Anaesthesia, 127 (6): 845–861 (2021)

doi: 10.1016/j.bja.2021.06.048
Advance Access Publication Date: 12 August 2021
Review Article

CARDIOVASCULAR

Heterogeneous impact of hypotension on organ perfusion and outcomes: a narrative review

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Summary

Arterial blood pressure is the driving force for organ perfusion. Although hypotension is common in acute care, there is a lack of accepted criteria for its definition. Most practitioners regard hypotension as undesirable even in situations that pose no immediate threat to life, but hypotension does not always lead to unfavourable outcomes based on experience and evidence. Thus efforts are needed to better understand the causes, consequences, and treatments of hypotension. This narrative review focuses on the heterogeneous underlying pathophysiological bases of hypotension and their impact on organ perfusion and patient outcomes. We propose the iso-pressure curve with hypotension and hypertension zones as a way to visualize changes in blood pressure. We also propose a haemodynamic pyramid and a pressure–output–resistance triangle to facilitate understanding of why hypotension can have different pathophysiological mechanisms and end-organ effects. We emphasise that hypotension does not always lead to organ hypoperfusion; to the contrary, hypotension may preserve or even increase organ perfusion depending on the relative changes in perfusion pressure and regional vascular resistance and the status of blood pressure autoregulation. Evidence from RCTs does not support the notion that a higher arterial blood pressure target always leads to improved outcomes. Management of blood pressure is not about maintaining a prespecified value, but rather involves ensuring organ perfusion without undue stress on the cardiovascular system.

Keywords: autoregulation; blood pressure; hypotension; organ perfusion; outcome; pathophysiology; perfusion

Editor's key points

- Hypotension has heterogenous underlying pathophysiological causes and organ-specific effects on tissue perfusion.
- Hypotension does not always lead to organ hypoperfusion; in fact, it may not affect or may even increase organ perfusion.
- The overall evidence from RCTs does not support the notion that a higher blood pressure target always leads to improved patient outcomes.

Arterial BP is perhaps the most commonly measured haemodynamic variable. It can increase or decrease acutely to produce hypertension or hypotension, respectively. Although the terms hypertension and hypotension have long been in use, widely accepted criteria defining them in acute care, including in the perioperative, intensive care, and emergency settings, have not been established. This is exemplified by the fact that although the diagnostic criteria for chronic hypertension are defined in chronic care,[1,2] although diagnostic criteria have recently been revised,[3] similar clearly defined criteria for acute hypertension in acute care do not exist (but see Sessler and colleagues[4] for recent efforts to establish such criteria). This review focuses on the discussion of acute hypotension, which is a more frequent occurrence than acute hypertension in acute care.

Hypotension currently lacks widely accepted criteria for diagnosis in acute care.[5,6] A cohort study showed that both the threshold used to define hypotension and the method chosen to quantify hypotension affect the association between intraoperative hypotension and outcomes.[7] This finding suggests that intraoperative hypotension studies

Received: 7 April 2021; **Accepted:** 25 June 2021

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based on different methodologies are not comparable and that it is challenging to apply the reported results in clinical practice. Although hypotension does not always appear to be hazardous based on both clinical experience and available evidence, most practitioners still regard it as undesirable, even in situations that pose no immediate threat to life. This incongruity implies that we may need to reflect on the fundamentals of hypotension, including its underlying pathophysiology and critical impact. Clarification of these fundamentals may improve our understanding of acute hypotension in acute care.

Hypotension and outcomes based on cohort studies

Most cohort studies show a consistent association between acute hypotension and unfavourable outcomes in acute care.[8,9] For example cohort studies performed in noncardiac non-neurologic surgical patients show an association between perioperative hypotension and unfavourable outcomes, namely mortality,[10–25] all-cause morbidity,[26] acute kidney injury,[27–32] myocardial injury,[11,19,27,29,30,33–39] congestive heart failure,[40] stroke,[25,39,41] cognitive decline,[42] delirium,[43] poor liver[8] and kidney[44] graft function, and postoesophagectomy leak.[45] However, there are exceptions in which no association between hypotension and unfavourable outcomes was found for noncardiac non-neurologic surgical patients.[46–50] Similarly, most cohort studies performed in cardiac surgical patients involving cardiopulmonary bypass show an association between perioperative hypotension and increased mortality,[51,52] major morbidity,[52] watershed stroke,[53] early cognitive dysfunction,[54] postoperative delirium,[55] and acute kidney injury.[56–58] However, there are exceptions in this patient population as well: one study failed to associate hypotension with postoperative delirium,[59] and three studies failed to associate hypotension with acute kidney injury.[60–62]

The results of these cohort studies should be interpreted in light of their inherent limitations. The first limitation is related to the variety of thresholds used to define hypotension and the methods chosen to quantify the accumulative effects of hypotension (i.e. the exposure).[5,7] The variety in exposure definitions affects the results of the association between intraoperative hypotension and outcomes.[7] Moreover, the baseline BP used in retrospective studies might be unreliable as BP has a circadian fluctuation[63] and also tends to be higher in clinical/hospital settings (white coat hypertension).[64] The second limitation is related to the definition of outcomes. The outcomes, defined retrospectively, were not pre-specified, leading to variations in the timing, criteria, validity, relevance, and availability of the different outcome measures. The third limitation is related to confounder control. Hypotension has different underlying pathophysiological causes and effects on organ perfusion (see below), and organ perfusion, not the blood pressure *per se*, determines outcomes relevant to haemodynamics. Cohort studies investigating intraoperative hypotension do not normally consider flow/perfusion-related information (owing to the lack of routine measurement); therefore, these studies could be confounded by this unmeasured yet critical information. How hypotension is treated could also confound cohort studies because different treatments, although they may all increase BP, may have different effects on organ perfusion and other variables.[65]

Hypotension and outcomes based on randomised controlled trials

Among studies investigating the relationship between hypotension and outcomes, there is a conspicuous discrepancy between evidence based on cohort studies and evidence based on RCTs. Although an abundance of cohort studies have suggested an association between perioperative hypotension and unfavourable outcomes,[4] RCTs have failed to demonstrate consistently improved outcomes from maintaining a higher BP (Table 1).[66–73] Assessing this body of evidence in surgical patients is limited by: (1) different surgeries, (2) different BP targets and different BP-related interventions, (3) different outcome measures, and (4) different flow/perfusion (including pump flow during cardiopulmonary bypass). In patients with septic shock requiring resuscitation, there was no significant difference in mortality between strategies targeting a higher (80–85 mm Hg) or lower (65–70 mm Hg) MAP.[74] In critically ill older patients with vasodilatory hypotension, there was no significant difference in mortality between permissive hypotension (targeting an MAP of 60–65 mm Hg) and usual care (targeting a higher BP).[75] These inconsistent findings, albeit likely to have multifactorial causes, suggest that we may need an improved approach toward understanding hypotension, including its definition, pathophysiology, and effects on organ perfusion and patient outcomes, in acute care. In other words, BP management is not as simple as merely targeting a prespecified BP value.

Nature of blood pressure

Understanding the nature of BP helps to clarify when and why hypotension is worrisome. BP is the force exerted by the circulating blood that propels blood through the tissues and organs, that is organ perfusion, especially to the brain because it is at a higher level relative to the heart in sitting or standing individuals. Higher BP is required for the increased height difference between the brain and heart, as illustrated by the remarkably different baseline BP between standing giraffes and humans (systolic BP, ~300 *vs* ~120 mm Hg).[76]

Hypotension has different underlying pathophysiological mechanisms

Arterial blood pressure is the result of multiple haemodynamic elements (Fig. 1).[77] Therefore, hypotension is not always equivalent because it can have different underlying pathophysiological mechanisms as a result of different combinations of changes in relevant factors. The variety of potential underlying pathophysiological mechanisms based on the haemodynamic pyramid framework is presented in Figure 1. However, we use a simpler pressure–output–resistance triangle framework that regards BP as the product of cardiac output (CO) and systemic vascular resistance (SVR) (Fig. 2a).

BP is determined primarily by stroke volume (or CO) and SVR at a given filling pressure, for example central venous

Table 1 RCTs comparing a higher BP target with a lower BP target in perioperative care. *Early termination. CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; DWI, diffusion-weighed magnetic resonance imaging.

Year (Authors)	Surgery	Patients (n)	Higher BP target	Lower BP target	Outcomes	Conclusion
Noncardiac surgery						
1999 (Williams-Russo and colleagues)[73]	Hip surgery under epidural anaesthesia	235	MAP=55–70 mm Hg	MAP=45–55 mm Hg	Cognitive, cardiac and renal complications	No difference
2016 (Carrick and colleagues)[66,*]	Laparotomy or thoracotomy for trauma	168	MAP=65 mm Hg	MAP=50 mm Hg	30 day mortality	No difference
2017 (Futier and colleagues)[67]	Major abdominal surgery	292	SBP=90–110% of resting value	SBP >80 mm Hg or 60% of resting value	A composite of systemic inflammatory response syndrome and organ dysfunction by day 7 after surgery	A higher BP target is beneficial
Cardiac surgery						
1995 (Gold and colleagues)[68]	CABG with CPB	248	MAP=80–100 mm Hg during CPB	MAP=50–60 mm Hg during CPB	Mortality, cardiac, neurologic, and cognitive complications, and changes in quality of life	A higher MAP during CPB is beneficial
2007 (Charlson and colleagues)[70]	CABG with CPB	412	MAP target=80 mm Hg during CPB	MAP target=pre-bypass level during CPB	Mortality, major neurologic or cardiac complications, cognitive complications or deterioration in functional status	No difference
2011 (Siepe and colleagues)[69]	CABG with CPB	92	MAP=80–90 mm Hg during CPB	MAP=60–70 mm Hg during CPB	Early postoperative cognitive dysfunction and delirium	A higher MAP during CPB is beneficial
2014 (Azau and colleagues)[71]	Cardiac surgery with CPB	300	MAP=75–85 mm Hg during CPB	MAP=50–60 mm Hg during CPB	Acute kidney injury	No difference
2018 (Vedel and colleagues)[72]	Cardiac surgery with CPB	197	MAP=70–80 mm Hg during CPB	MAP=40–50 mm Hg during CPB	Cerebral infarcts detected by DWI	No difference

pressure (CVP); the relationship among these variables is governed by the equation $CO \times SVR = (MAP - CVP) \times 80$ (Fig. 3).[80] Thus BP can be the same for different CO and SVR values as long as the CO-SVR products are the same. For a constant CO-SVR product, the curve formed by different CO and SVR pairs (with different values) is referred to here as the iso-pressure curve (Fig. 3). The areas below and above the iso-pressure curve are referred to as the hypotension and hypertension zones, respectively (Fig. 3). The concepts of the iso-pressure curve and the hypotension and hypertension zones are explained in Figure 3. Hypotension has the following five exclusive underlying pathophysiological mechanisms based on different changes in CO and SVR (Figs 2 and 3):

- SVR decreases whereas CO remains stable (Fig. 2b).
- SVR decreases whereas CO increases, but the effect of the SVR decrease exceeds the effect of the CO increase (Fig. 2c).
- CO decreases whereas SVR remains stable (Fig. 2d).
- CO decreases whereas SVR increases, but the effect of the CO decrease surpasses the effect of the SVR increase (Fig. 2e).
- Both CO and SVR decrease (Fig. 2f).

Although each of these mechanisms leads to hypotension, they have different impacts on organ perfusion, as discussed in the following section.

This simplified approach should not distract our attention from the causes of changes in CO and SVR as they themselves have different determinants (Fig. 1). CO is the product of HR and stroke volume (SV), with SV dependent on preload, myocardial contractility, and afterload. SVR is determined by the vascular radius, vascular length, and blood viscosity. Clinically, interventions such as the administration of vasopressors,[65] beta-adrenergic antagonists,[81] and calcium channel blockers[82] and the use of pacemakers,[83] can lead to changes in these haemodynamic aspects, and therefore BP changes.

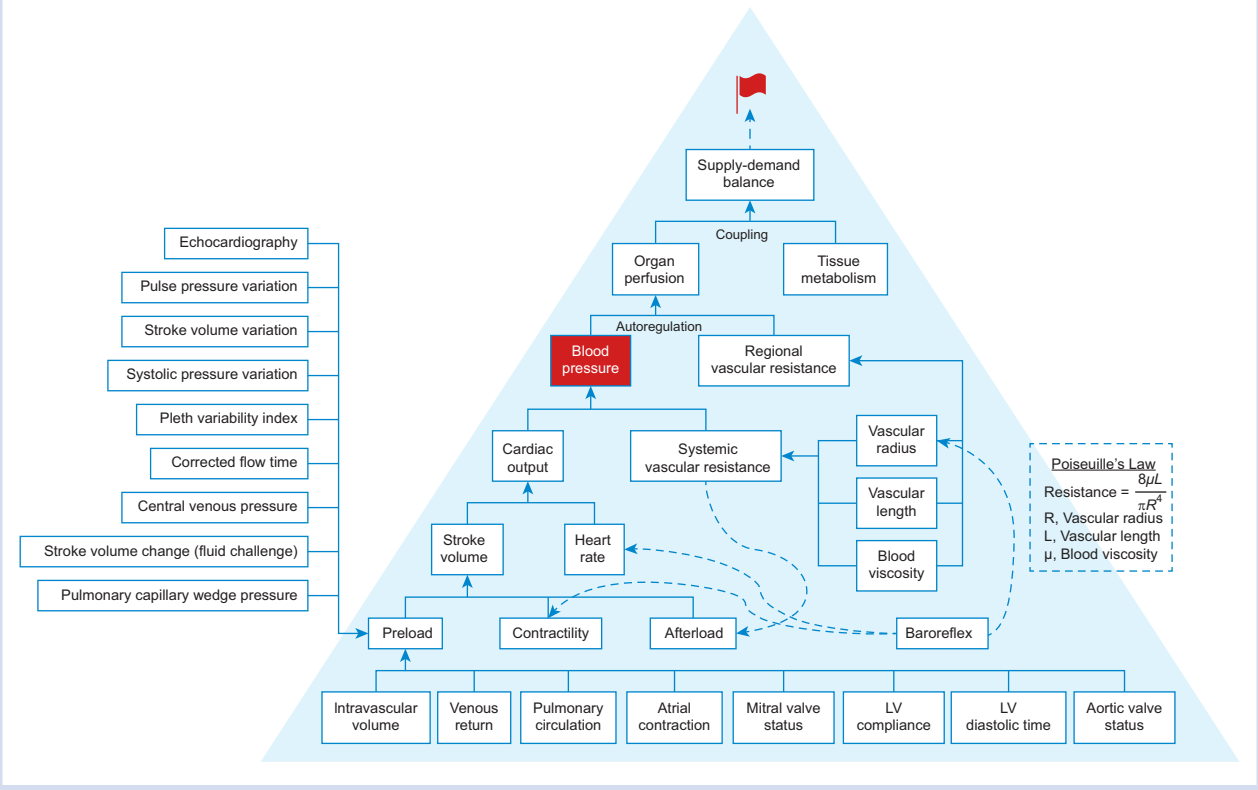

Fig 1. Haemodynamic pyramid. Venous blood must return to the heart and flow through the right heart, pulmonary vasculature, left atrium, and mitral valve to create the preload of the left ventricle. The magnitude of left ventricle preload is also dependent on atrial contraction, mitral valve status, aortic valve status (e.g. aortic valve regurgitation leading to augmented preload), and the compliance and diastolic time of the left ventricle. The magnitude of stroke volume is dependent on preload, myocardial contractility, and afterload. Blood pressure is dependent on cardiac output and systemic vascular resistance (SVR), whereas cardiac output is the product of stroke volume and heart rate. Afterload and SVR are related. SVR is proportional to the vascular length and blood viscosity and inversely proportional to vascular radius to the fourth power, a relationship described by the Hagen–Poiseuille equation. Organ perfusion is dependent on blood pressure (or perfusion pressure) and regional vascular resistance (RVR). The relationship between organ perfusion pressure and RVR is governed by pressure autoregulation. The match between organ perfusion and tissue metabolic activity determines perfusion adequacy and is one of the premises of organ well-being. Adequate organ perfusion is the primary goal of haemodynamic management. Baroreflex exerts its effects primarily on the vascular radius, heart rate, and myocardial contractility. Blood pressure (highlighted in red fonts) and heart rate are always monitored in acute care. The modern haemodynamic monitor enables the assessment of stroke volume and thus cardiac output or index. Tissue oximetry based on near-infrared spectroscopy enables assessing the balance between tissue oxygen consumption and supply. A variety of means and parameters assesses preload. Modern haemodynamic management has a variety of approaches with likely different effectiveness depending on the outcomes of interest.[77–79] LV, left ventricle.

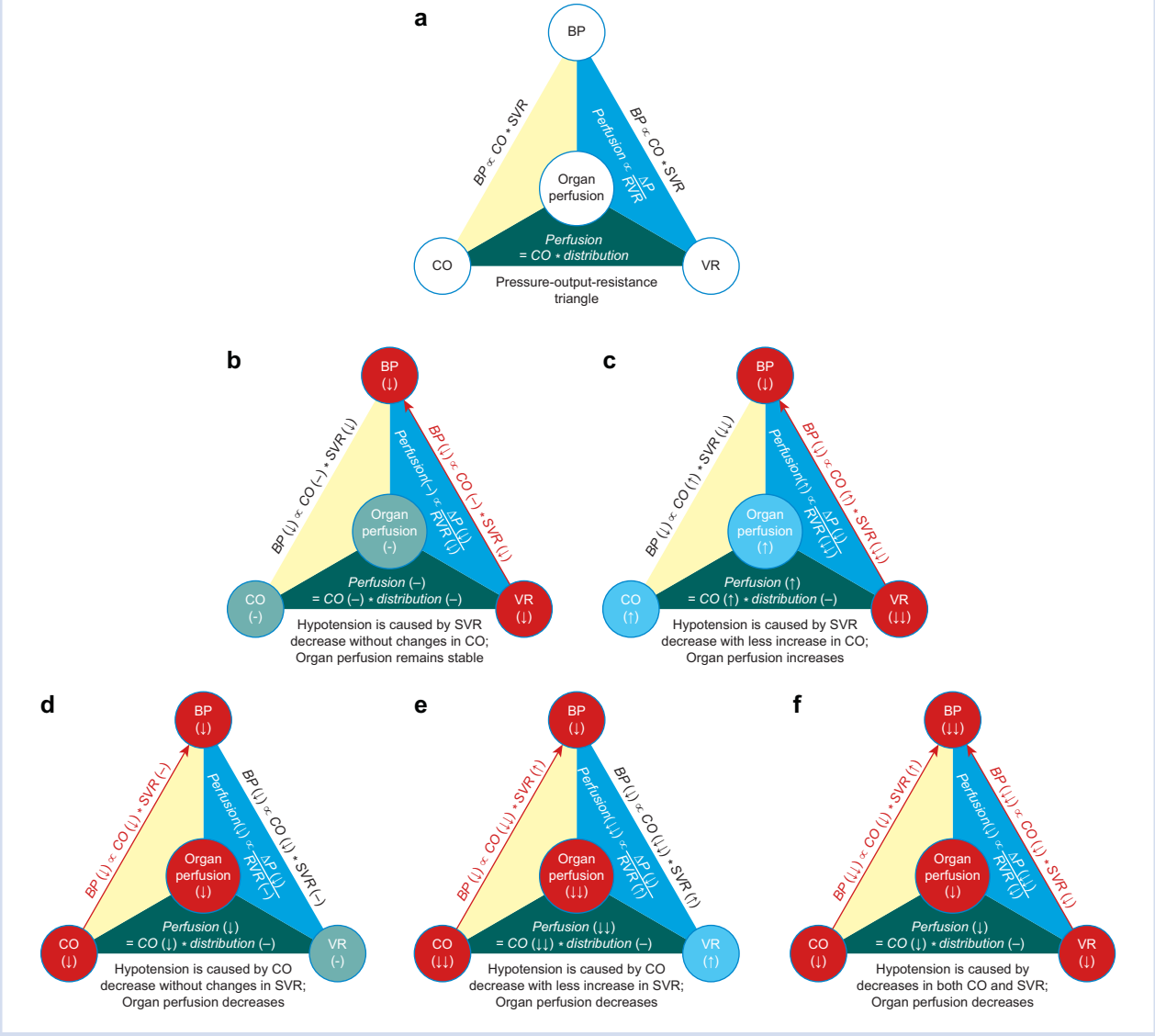

Fig 2. The pressure–output–resistance triangle. Organ perfusion is in the centre of the triangle. This diagram is based on the following premises: (1) changes in systemic vascular resistance (determinant of blood pressure) and regional vascular resistance (determinant of organ perfusion) are concordant, and (2) the share of cardiac output among various organs remains stable. Blood pressure is proportional to cardiac output and systemic vascular resistance. Organ perfusion is proportional to perfusion pressure and inversely proportional to regional vascular resistance; it is also a percentage share of cardiac output (a). Hypotension can be caused by a decrease in systemic vascular resistance (close red circle and red arrow), and in this case, organ perfusion remains stable because of the proportional decreases in blood pressure and regional vascular resistance (b). Hypotension can be caused by a significant decrease in systemic vascular resistance (closed red circle and red arrow), although there is a lesser degree of increase in cardiac output (closed blue circle). In this case, organ perfusion is increased because of the lesser decrease in blood pressure than the decrease in regional vascular resistance (c). Hypotension can be caused by a decrease in cardiac output (closed red circle and red arrow), and in this case, organ perfusion is decreased because of decreased perfusion pressure in the face of an unchanged regional vascular resistance (d). Hypotension can be caused by a significant decrease in cardiac output (closed red circle and red arrow), although there is a lesser degree of increase in systemic vascular resistance (closed blue circle). In this case, organ perfusion has a significant decrease because of decreased perfusion pressure in the face of an increased regional vascular resistance (e). Hypotension can be caused by simultaneous decreases in cardiac output and systemic vascular resistance (closed red circles and red arrows). In this case, organ perfusion is decreased because of the more significant decrease in perfusion pressure than the decrease in regional vascular resistance (f). CO, cardiac output; VR, vascular resistance which can be either SVR (systemic vascular resistance) or RVR (regional vascular resistance) depending on the context; ΔP, perfusion pressure.

Organ-specific impact of hypotension on perfusion

Hypotension, although usually leading to decreased perfusion pressure, does not always lead to organ hypoperfusion because organ perfusion is determined by the perfusion pressure divided by the regional vascular resistance (RVR). Based on Poiseuille's law, RVR is determined by the vascular radius, vascular length, and blood viscosity, although the vascular length rarely changes clinically. Multiple factors can change the vascular radius or vasomotor tone, for example age, atherosclerosis, blood pressure, hypercapnia, and vasoactive drugs (to name a few), and thus lead to RVR changes. The change in vasomotor tone secondary to a change in perfusion pressure is mediated by the myogenic mechanism and is the foundation of the pressure-dependent autoregulation of organ blood flow (Fig. 4). Depending on the relative direction and magnitude of changes in RVR as compared with perfusion pressure, hypotension can have the following three effects on organ perfusion:

- Organ perfusion remains *stable* if the effects of the decreases in perfusion pressure and RVR are comparable, a scenario in which the underlying pathophysiology of hypotension is an SVR decrease without changes in CO (Fig. 2b). This impact is consistent with the conventional concept of pressure autoregulation, as discussed in the following section.
- Organ perfusion *increases* if the effect of the perfusion pressure decrease is less than that of the RVR decrease, a scenario in which hypotension is secondary to an SVR decrease accompanied by a lesser degree of CO increase (Fig. 2c), as exemplified by the use of certain calcium channel blockers.[82]

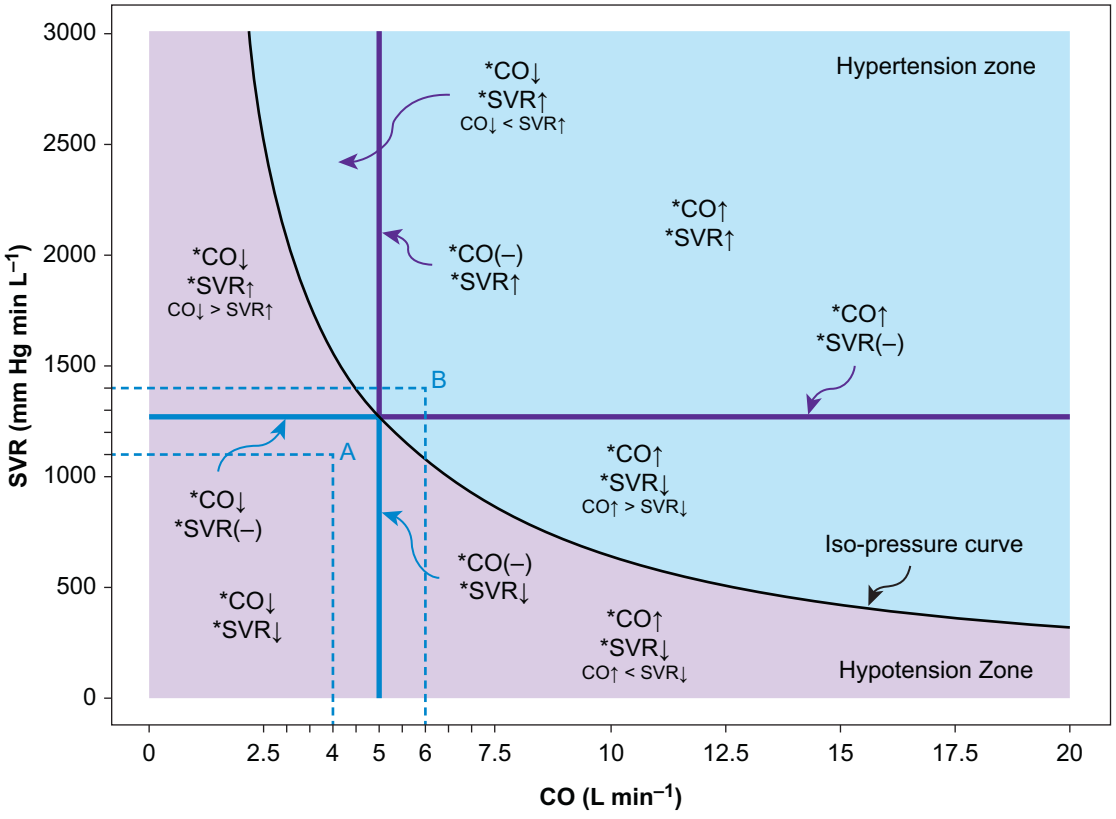

Fig 3. Hypotension and hypertension zones divided by the iso-pressure curve. The abscissa indicates CO, and the ordinate indicates SVR. The following equation governs the relationship among different systemic haemodynamic variables: CO × SVR = (MAP − CVP) × 80. The black curve is the iso-pressure curve; for a given pair of CO and SVR values, as long as the CO–SVR product equals the difference of MAP and CVP times 80, the point determined by the CO–SVR pair falls on the iso-pressure curve. In this case, we assume MAP is 85 mm Hg and the CVP is 5 mm Hg to exemplify the concept; the point representing a CO of 5 L min^{-1} and an SVR of 1280 mm Hg min L^{-1} falls on the black iso-pressure curve because the CO-SVR product equals the MAP–CVP difference times 80. The left lower purple area is called the hypotension zone because any point in this area, no matter what CO and SVR values it presents, leads to a smaller MAP–CVP difference than the MAP-CVP difference dictating the iso-pressure curve. For example, point A, determined by a CO of 4 L min^{-1} and an SVR of 1100 mm Hg min L^{-1}, corresponds to a MAP–CVP difference of approximately 55 mm Hg; if assuming CVP equals 5 mm Hg, MAP is 60 mm Hg in this example. The combinations of different CO and SVR changes represent different underlying pathophysiologies of hypotension. The right upper blue area is called the hypertension zone because any point in this area, no matter what CO and SVR values it represents, leads to a larger MAP–CVP difference than the MAP–CVP difference dictating the iso-pressure curve. For example, point B, determined by a CO of 6 L min^{-1} and an SVR of 1400 mm Hg min L^{-1}, corresponds to a MAP–CVP difference of approximately 105 mm Hg; if assuming CVP equals 5 mm Hg, the MAP is 110 mm Hg in this example. The combinations of different CO and SVR changes represent different underlying pathophysiologies of hypertension. CO, cardiac output; SVR, systemic vascular resistance; CVP, central venous pressure.

- Organ perfusion *decreases* if perfusion pressure decreases in the face of one of the following changes in RVR: (1) an unchanged RVR – that is a scenario in which the underlying pathophysiology of hypotension is a CO decrease without changes in SVR (Fig. 2d); (2) an increased RVR – that is a scenario in which hypotension is secondary to a CO decrease accompanied by a lesser degree of SVR increase (Fig. 2e); or (3) a decreased RVR, with the degree of the RVR decrease less than that of the perfusion pressure decrease – a scenario in which hypotension is secondary to a decrease in both CO and SVR (Fig. 2f).

The overarching message is that hypotension does not inevitably lead to a decrease in organ perfusion; instead, its impact on organ perfusion is dependent on the direction of the change in RVR (i.e. no change, increase, or decrease) and, when RVR decreases, on the relative decrease in RVR in comparison with the decrease in perfusion pressure. The lack of organ perfusion appraisal may be a reason for the inconsistent results among the abovementioned studies investigating the relationship between hypotension and outcomes in acute care. After all, these studies were based on outcomes that were largely determined by organ perfusion.

Organ blood flow regulation

Organ blood flow regulation can be better explained at the level of tissue microcirculation. The regulation of tissue microcirculation takes place at the level of arterioles where capillary perfusion starts.[85] Arterioles can dilate and constrict thanks to the smooth muscle in the arteriolar wall, which leads to changes in the arteriolar radius. This is a much more robust and efficient way of flow resistance adjustment compared with changes in vascular length or blood viscosity, because resistance is inversely proportional to vascular radius to the fourth power, but only directly proportional to vascular length and blood viscosity to the first power, per Poiseuille's law. Multiple factors regulate tissue perfusion via arteriolar dilation and constriction, including (1) perfusion pressure (i.e. pressure autoregulation), (2) the autonomic nervous system, (3) circulating hormones, (4) local metabolic activity, (5) endothelial products, and (6) flow-mediated diameter changes.[85] The amalgamation of the effects exerted by these vasomotor tone modulators sets the flow resistance and regulates downstream capillary perfusion.

The capillary bed itself can also regulate its own perfusion. Endothelial cells possess contractile fibres and are able to

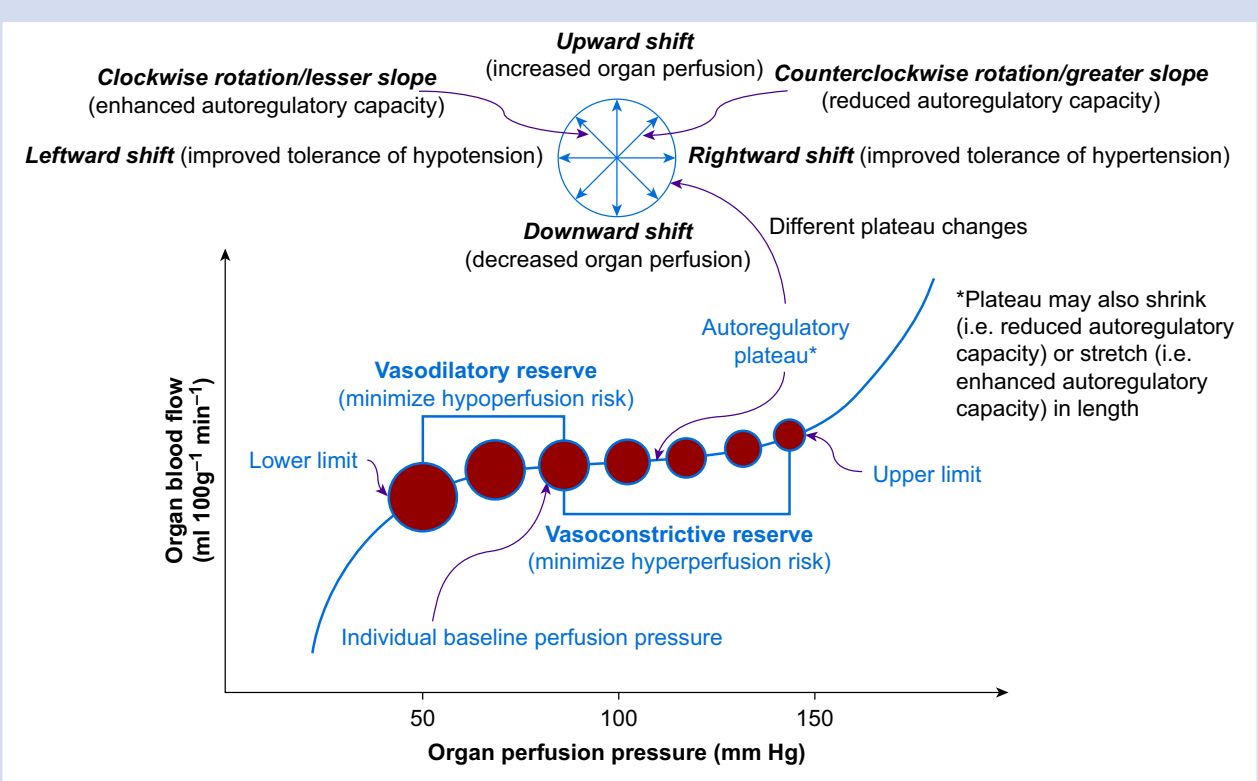

Fig 4. Pressure autoregulation of organ perfusion. The abscissa represents organ perfusion pressure whereas the ordinate represents organ blood flow. The relationship between organ perfusion pressure and blood flow is depicted by the autoregulation curve (blue curve), with the lower limit, upper limit, and plateau indicated. Organ blood flow remains relatively stable via active vasodilation or vasoconstriction (indicated by the closed red circles with different sizes) when organ perfusion pressure falls within the range between the lower and upper limits (i.e. the plateau). Each individual has a baseline blood pressure, and thus, a baseline perfusion pressure for each organ. When organ perfusion pressure decreases, organ vasculature responsible for flow resistance dilates to minimise hypoperfusion/ischaemia (vasodilatory reserve); otherwise, when organ perfusion pressure increases, organ vasculature responsible for flow resistance constricts to minimise hyperperfusion (vasoconstrictive reserve). The capacity of pressure autoregulation is organ-dependent. Multiple factors can affect the position and shape of the autoregulatory curve, as indicated by the compass.[84]

regulate their volume in response to external stimuli.[86] Evidence also suggests that capillaries respond to changes in BP, such that capillary diameter decreases during hypotension to the extent that red blood cell transit stops.[87]

Pressure autoregulation, which maintains relatively stable organ perfusion despite fluctuating perfusion pressure, is just one mechanism of organ blood flow regulation (Fig. 4).[84,88,89] Viewing pressure autoregulation in the context of non-pressure regulatory mechanisms can be perplexing. There are two ways to consider the interplay between pressure autoregulation and non-pressure regulatory mechanisms. One way is to regard them as coexisting or parallel mechanisms, with organ perfusion as the end result of their summation. The other way is to consider non-pressure regulatory mechanisms as factors that modulate pressure autoregulation[89]; for example hypercapnia (i.e. a metabolite) regulates pressure autoregulation by shortening the plateau and shifting it upwards.[88] Besides the interplay with non-pressure regulatory mechanisms, pressure autoregulation is also affected by physiological factors (e.g. age), chronic disease (e.g. hypertension and atherosclerosis), acute illness (e.g. traumatic brain injury), anaesthetics (e.g. sevoflurane), and drugs (e.g. calcium channel blockers).[84] Moreover, different organs have different pressure autoregulation capacities, and what are commonly considered vital organs (brain, heart, and kidney) are equipped with robust autoregulatory capacities.[84] Pressure autoregulation renders mammals, and especially their vital organs, more tolerant to acute hypotension and hypertension. During hypotension, the stable organ perfusion rendered by pressure autoregulation is consistent with the scenario described in Figure 2b (comparable reductions in perfusion pressure and RVR).

During sepsis and shock, macrocirculation and microcirculation are uncoupled despite the presence of normalised systemic haemodynamic variables.[90] This concept is supported by the finding that sublingual capillary microvascular flow and the percentage of perfused capillaries remain unchanged despite an increase of MAP from 65 to 85 mm Hg using vasopressor infusion in septic shock patients.[91,92] Microcirculatory dysfunction and mitochondrial depression are prominent pathophysiological features underlying the conditions of sepsis and shock and are responsible for refractory regional hypoxia and oxygen extraction deficit despite the correction of global oxygen delivery variables.[93] Whether therapies aimed at microcirculation recruitment, such as using nitric oxide donors to open the hypoperfused capillary bed or increasing the opening pressure of microcirculation, or goal-directed therapy of microcirculation guided by tissue oxygen monitoring,[94] improve outcomes remains to be determined.[95]

Importance of cardiac output to organ perfusion

The preceding discussion highlighted that CO is not only a determinant of BP but also associates with organ perfusion. Although BP decreases in every scenario, organ perfusion likely remains stable when CO remains stable (Fig. 2b), organ perfusion likely increases when CO increases (Fig. 2c), and organ perfusion likely decreases when CO decreases (Fig. 2d–f). This observation can be better comprehended if viewing organ perfusion as a percentage share of CO because CO is ultimately distributed to various tissues and organs and the summation of their perfusion shares equals CO.[89] This view of the relationship between CO and organ perfusion enriches the traditional view regarding organ perfusion as the perfusion pressure divided by the RVR. It also highlights the importance of monitoring and maintaining CO when the ultimate goal is to ensure organ perfusion. However, we caution that this view of the relationship between CO and organ perfusion may not be applicable in conditions such as sepsis and shock, where microcirculatory dysfunction and the macrocirculation–microcirculation uncoupling are prominent features.

There is evidence suggesting the importance of maintaining CO in noncardiac surgical patients. In older adults (mean age 72 yr) with comorbid conditions undergoing elective total hip surgery with epidural anaesthesia, maintaining intraoperative MAP in the range of 45–55 mm Hg or 55–70 mm Hg did not lead to different outcomes (cognitive, cardiac, renal, and thromboembolic complications).[73] One potential explanation for this result was the maintained CO in patients from both groups because all patients received a low-dose i.v. epinephrine infusion. Other studies showed that epinephrine infusion at rates of 1–5 μg min^{-1} preserves or augments CO despite significant hypotension.[96,97] In high-risk patients aged 50 yr or older undergoing major gastrointestinal surgery, an RCT of the effects of usual care or perioperative CO-guided haemodynamic management on a composite of predefined 30 day moderate or major complications and mortality[98] showed that CO-guided management through targeting a maximal SV via i.v. colloid infusion with a fixed low-dose dopexamine infusion (0.5 μg kg^{-1} min^{-1}) led to reduction in the primary outcome (36.6%) compared with usual care (43.4%), although this difference did not reach a statistical significance ($P=0.07$).[98]

The importance of CO in organ perfusion was corroborated by an RCT performed in cardiac surgical patients,[72] which showed that, targeting a higher MAP (70–80 mm Hg), compared with targeting a lower MAP (40–50 mm Hg), during cardiopulmonary bypass did not lead to significantly different volumes or numbers of new cerebral infarcts.[72] A 40–50 mm Hg MAP is equivalent to a 30–40 mm Hg cerebral perfusion pressure assuming an intracranial pressure of 10 mm Hg (i.e. cerebral perfusion pressure equals MAP − intracranial pressure). A cerebral perfusion pressure of 30–40 mm Hg is much lower than 65 mm Hg, the widely quoted lower limit of cerebral autoregulation.[88] Therefore, not seeing a worse cerebral outcome associated with this dangerously low MAP is counterintuitive. Amidst this perplexity, the most plausible explanation is how the pump flow (the equivalent of CO during cardiopulmonary bypass) was managed: it was fixed at 2.4 L min^{-1} m^{-2} irrespective of the target MAP. Therefore, if the pump flow's distribution to the brain remained unchanged, the brain would not become ischaemic despite a much lower MAP.

In contrast, an RCT performed in patients undergoing moderate-risk abdominal surgery showed that cardiac index and pulse pressure variation-guided haemodynamic therapy, on top of MAP-guided therapy, did not lead to improved composite outcomes compared with MAP-guided therapy only.[99] There are several explanations for this finding. First,

the intervention protocols (i.e. exposures) were not distinctively different between the groups. The end result of cardiac index and pulse pressure variation-guided care was the maintenance of the targeted BP via informed intravascular volume management; however, the same BP was also targeted and accomplished in the control group. Second, the composite outcome included complications with different severities and different relevance to haemodynamics, which may decrease the power of detecting a between-group difference.[100] Third, the patients were undergoing moderate-risk abdominal surgery, and thus may have benefited from advanced haemodynamic therapy differently compared with patients undergoing high-risk surgeries.[101] However a recent sub-analysis of the Crystalloid–Colloid Study found that the worse outcomes associated with hypotension were independent of cardiac index in noncardiac surgery patients.[102]

Proposed definition and classification of hypotension

In light of the preceding discussion, hypotension is a systemic haemodynamic abnormality, defined as a measured blood pressure that is lower than a prespecified threshold, that is directly caused by changes in CO, SVR, or both, and that may or may not lead to organ and tissue hypoperfusion. There are different working definitions of hypotension; we advocate a definition that is easy to apply and relevant to patient outcomes. Thus different hypotension criteria should be established for different patient populations.[4,8]

In light of the different effects of hypotension on organ perfusion, we propose further classification of hypotension as (1) concerning: hypotension that leads to decreased organ perfusion; (2) possibly concerning: does not lead to decreased organ perfusion; and (3) questionable: the impact on organ perfusion cannot be confidently determined. Although a number conventionally defines hypotension, the perfusion/demand match defines whether or not hypotension is concerning.

Organ perfusion assessment

Reliable assessment of organ perfusion facilitates hypotension management in acute care. However, organ perfusion assessment is challenging in clinical practice as no monitor exists that can directly quantify the blood flow to a specific organ. Instead, indirect methods are currently used for organ perfusion assessment (Supplementary Table S1). Signs and symptoms occur because of organ ischaemia, such as chest pain during myocardial ischaemia and dizziness during cerebral ischaemia; these are commonly used clinically for organ perfusion assessment. Monitoring and laboratory studies are available for diagnosing organ ischaemia with varying sensitivities and specificities, such as changes in electrocardiography and troponin elevation for myocardial ischaemia. An emerging technology is tissue oximetry based on near-infrared spectroscopy, which assesses the balance between tissue oxygen consumption and supply in the tissue bed illuminated by near-infrared lights.[65,103] This monitor is noninvasive, continuous, portable, and can be applied to different organs.[65,104,105] However, tissue oxygenation measured by near-infrared spectroscopy reflects tissue perfusion only when tissue metabolic rate of oxygen remains relatively stable.[106] Other technologies, such as sidestream darkfield imaging[91] and orthogonal polarisation spectral imaging,[107] have also been used for microcirculation assessment.

Clinical scenarios involving hypotension

These examples highlight the complexity of real-world practice and underline the importance of the critical appraisal of hypotension in acute care.

Beta blocker-related hypotension

Perioperative use of beta blockers in noncardiac surgical patients is associated with increased incidence of hypotension.[25,108,109] Reduced CO secondary to reduced HR and SV is primarily responsible for beta blocker-related hypotension, especially when using beta blockers that do not have intrinsic sympathomimetic activity.[111] Although there may be a decrease in coronary perfusion pressure because of hypotension, beta blockers may augment coronary blood flow by increasing diastolic perfusion time via HR slowing[112] or by coronary vasodilation.[113] The level I recommendation for initiating oral beta blockers within the first 24 h in patients with non-ST-elevation acute coronary syndromes in the absence of heart failure, low-output state, risk of cardiogenic shock, or other contraindications highlights beta blockers' beneficial effect on the myocardial metabolic demand–supply balance.[114] Propranolol can significantly reduce cerebral perfusion pressure and cerebral blood flow, although it also reduces cerebral metabolic rate of oxygen in baboons.[115] In contrast, use of labetalol, metoprolol, oxprenolol, and sotalol did not lead to significant changes in cerebral blood flow in hypertensive patients.[116] Perioperative use of beta blockers initiated 1 day or less before noncardiac surgery reduces nonfatal myocardial infarction but increases the risk of stroke and death.[25,109] The role of hypotension in this outcome remains unclear.

Nicardipine-related hypotension

Nicardipine is widely used as an antihypertensive drug in acute care because of its efficiency, predictability, and titratability.[82] Although it is a powerful arteriodilator and afterload/SVR/RVR modulator, nicardipine does not typically decrease preload or adversely affect myocardial contractility.[82,117–120] It increases CO because of an increase in HR and SV.[82,117–120] Nicardipine augments organ perfusion, as evidenced by increased coronary,[119,120] cerebral,[121] renal,[122] vertebral,[122] and skeletal muscle blood flow.[82] In the face of decreased BP, the increased organ perfusion suggests that the degree of RVR decrease exceeds the degree of BP decrease (Fig. 2c). Whether nicardipine's haemodynamic profile leads to improved outcomes remains to be determined.

Hypotension related to angiotensin converting enzyme inhibitors or angiotensin II receptor blockers

Observational studies suggest that continuing angiotensin converting enzyme inhibitors (ACEIs) on the day of surgery poses an increased risk of intraoperative hypotension.[123] Although some studies show a relatively stable CO,[124,125] a meta-analysis noted a CO increase after ACEIs/angiotensin II receptor blockers (ARBs) administration,[126] and there is

evidence supporting both withholding[127] and continuation[128,129] of ACEIs/ARBs before surgery. A meta-analysis based on five RCTs and four cohort studies failed to demonstrate an association between perioperative use of ACEIs/ARBs and mortality or major cardiac events.[123] The 2014 American College of Cardiology/American Heart Association guidelines recommend continuing these treatments throughout the perioperative period.[130] Although continuation of ACEIs/ARBs perioperatively is associated with increased risk of hypotension, the overall evidence at present does not link this to unfavourable outcomes.

Neuraxial block-related hypotension

Hypotension is common after neuraxial block in obstetric and surgical patients. Neuraxial block-related hypotension is caused by a decrease in SVR, not CO. A study of patients undergoing elective Caesarean delivery showed that although systolic BP decreased 7% below baseline, CO increased 19% from baseline 20 min after the neuraxial block.[131] In patients undergoing hip surgery under hypotensive epidural anaesthesia (maintaining MAP $\leq$50 mm Hg while infusing epinephrine to support circulation), an observational study showed that cerebral blood flow velocity was well maintained, despite MAPs well below the commonly accepted lower limit of cerebral autoregulation.[132] However, there was considerable inter-individual heterogeneity, with 23% of patients having >20% reduction in cerebral blood flow velocity.[133] In patients with severe coronary artery disease, an observational study showed that high thoracic epidural anaesthesia did not change coronary perfusion pressure or myocardial blood flow.[133] This study also showed that thoracic epidural block increases the diameter of stenotic, but not non-stenotic, epicardial coronary artery segments.[133] In patients with ischaemic heart disease, high thoracic epidural analgesia was able to partly normalise the myocardial blood flow response to sympathetic stimulation.[134] When low-dose epinephrine was infused during epidural anaesthesia, patients who had a lower MAP (45–55 mm Hg) did not experience more complications than patients who had a higher MAP (55–70 mm Hg).[73] A population-based cohort study, using data from propensity score-matched patients, concluded that epidural anaesthesia is associated with a small reduction in 30 day mortality.[135] Therefore, the available evidence suggests that as long as extreme hypotension is avoided, neuraxial block-related hypotension does not appear to be harmful.

Acute anaemia-related hypotension

Acute anaemia leads to increased CO,[136] increased cerebral blood flow,[137] and increased coronary blood flow[138] as a compensatory mechanism to boost oxygen delivery when arterial blood oxygen content is reduced.[139] Acute anaemia also decreases blood viscosity and SVR.[136] There appears to be an interplay between changes in blood viscosity and changes in CO during acute anaemia.[136] Acute anaemia can lead to hypotension depending on the relative changes between CO and SVR. There was initially a concern that co-occurrence of anaemia and hypotension during cardiopulmonary bypass could be associated with an increased risk of postoperative acute kidney injury[60]; however, this was later refuted by a large cohort study.[61] In high-risk patients undergoing hip fracture repair, liberal transfusion (maintaining a haemoglobin >100 g L^{-1}) and restrictive transfusion (maintaining a haemoglobin no >80 g L^{-1} or keeping the patient free from anaemia-related symptoms) did not lead to different outcomes.[140,141] At present, there is no evidence attesting to adverse effects associated with acute anaemia-related hypotension.

Propofol-related hypotension

Hypotension is common after anaesthesia induction using propofol.[142] The effects of propofol on haemodynamics are mediated primarily via inhibition of sympathetic nervous activity, as opposed to direct vasomotor tone changes.[142] Propofol impairs baroreflex,[143] decreases SVR,[144] decreases venous return,[145] and can reduce CO.[144,146] The impact of propofol on organ perfusion varies between brain and other organs. Propofol reduces cerebral perfusion but does not cause ischaemia because of the proportional reduction in cerebral metabolic activity.[147–149] There is a lack of direct evidence on its effects on perfusion of non-brain organs, although indirect evidence suggests that it may not have adverse effects.[150] Propofol may cause some degree of CO reduction[144,146]; however, this may not be consequential. As propofol can cause up to a 30% decrease in cerebral blood flow,[147] it is likely that the reduced cerebral perfusion may be mainly responsible for the reduced CO because the brain accounts for up to 20% of CO.[151] At present, there is no evidence attesting to an adverse effect exerted by propofol-related hypotension.

Septic shock-related hypotension

Septic shock is characterised by distributive organ hypoperfusion in the face of hypotension, vasodilation, and, frequently, increased CO.[152–156] Several studies have found that when MAP is increased from 65 to 85 mm Hg using norepinephrine infusion in patients with septic shock, CO increases by 8–20%.[91,157–159] However, the increase in CO does not consistently translate into an increase in organ perfusion. Some studies show that norepinephrine infusion, which increased MAP from 65 to 85 mm Hg, did not improve tissue perfusion.[91,157,158] In contrast, other studies show that norepinephrine infusion leads to improved tissue perfusion.[159,160] Among the multiple potential reasons for this discrepancy, flow redistribution may be responsible for the inconsistent changes in tissue perfusion.[161,162] Even though an organ may appear to have sufficient gross perfusion, it can still undergo regional tissue ischaemia and hypoxia because of microcirculatory and mitochondrial dysfunction[93] or unmet hypermetabolic activity.[163] The challenges of treating haemodynamic abnormalities in septic shock were highlighted by a multicentre RCT,[74] which showed that targeting MAP of 80–85 mm Hg, as compared with 65–70 mm Hg, did not lead to differences in mortality at either 28 or 90 days.[74] Based on this, septic shock is neither caused by hypotension nor can it be cured by BP-increasing treatment.

Clinical implications

BP is the most common haemodynamic variable monitored in patient care (as a vital sign). Although HR is also monitored (as a vital sign), there is a consensus that it does not provide the same haemodynamic information as BP. The key message of the above discussion is the 'heterogeneity' of hypotension effects on underlying pathophysiology and its impact on organ perfusion and outcomes. The clinical management of

hypotension follows the axis of diagnosis–decision-making–intervention (Fig. 5); it is critical to remember that the goal is to ensure organ perfusion, not to correct a number.

The first step in managing hypotension is to determine whether the BP decreases below a prespecified threshold. This can be challenging, as in perioperative care, the thresholds used to define hypotension are primarily experience-based owing to the lack of convincing RCT-based evidence.[4,8] In critical care, the criteria for hypotension are also controversial and appear to depend on the patient population. The Surviving Sepsis Campaign recommends an initial target MAP of 65 mm Hg in patients with septic shock requiring vasopressors based on moderate-quality evidence.[156] In contrast, patients with acute ischaemic stroke mandate a much higher BP for brain perfusion, although the minimal BP that is acceptable remains to be determined.[164,165]

The second step in managing hypotension is decision-making, that is deciding whether the diagnosed hypotension requires treatment. The decision-making process must take the patient's baseline condition, the impact on organ perfusion, outcomes evidence, the nature of the procedure, and the surgeon's preference into consideration. This is a complicated process, and there is no single criterion that fits all scenarios. Haemodynamics need to be meticulously managed in patients at risk of organ ischaemia because of either arterial stenotic disease (e.g. coronary artery disease) or the procedure itself (e.g. carotid artery clamping for endarterectomy). If the surgeon insists on lowering BP during signs of organ ischaemia, the situation should be discussed with the surgeon, and an observation should be made regarding whether improving CO or decreasing organ metabolic demand can reverse organ ischaemia. The outcome evidence upon which the decision-making process is based needs to be consistent and free from significant bias and limitations. At present, existing evidence does not consistently support the notion that a higher BP target leads to improved outcomes. Individualised BP management is promising,[67] but challenges include what the baseline BP is and how to determine it.

It should be noted that different organs have different perfusion regulation and different tolerance of ischaemia.[84] For example the brain cannot tolerate even a few minutes of ischaemia,[166] whereas muscle can tolerate up to 2 h of ischaemia, as exemplified by the prevalent use of a tourniquet during limb procedures.[167] Therefore, the impact of hypotension on organ perfusion is also organ-dependent, and organs that have poor tolerance of ischaemia should be closely monitored and prioritised in haemodynamic management.[84]

The third step is intervention if the decision is to correct the hypotension. There are two different lines of approach for treatment of hypotension. One addresses the cause of the hypotension, including – but not limited to – transfusion if there is active bleeding, infusion if there is intravascular volume depletion, lightening anaesthesia if it is too deep, avoiding beta blockers, calcium channel blockers, ACEIs/ARBs, and

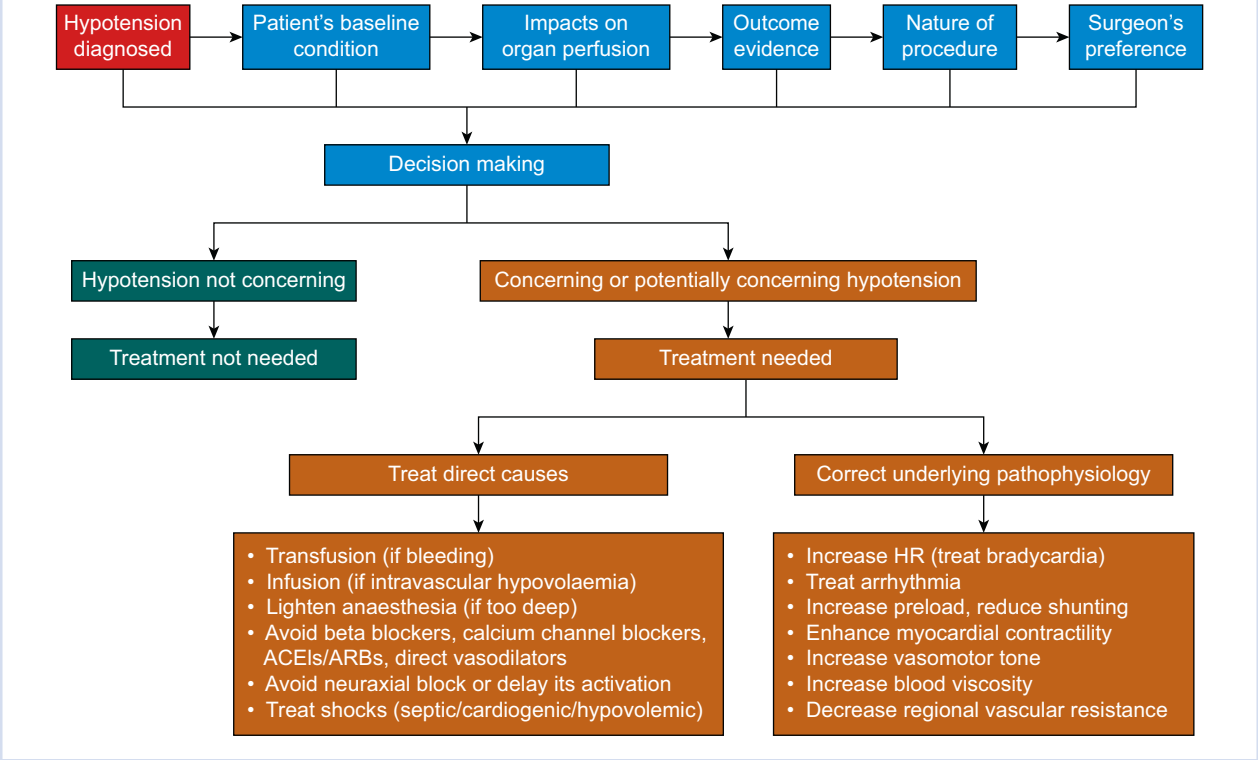

Fig 5. The axis of diagnosis–decision-making–intervention for hypotension management. The first step is to diagnose hypotension based on both clinical experience and the available consensus.[8] The second step is to decide to treat or not to treat hypotension, which is a complicated decision-making process that needs to take the patient's baseline condition, effects on organ perfusion, outcome evidence, and nature of the procedure. The third step is intervention if the decision is to treat hypotension. The intervention follows two approaches: one is to treat direct causes, and the other is to correct the underlying pathophysiology responsible for hypotension. These two lines of treatment approaches may sometimes overlap. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

direct vasodilators, avoiding neuraxial blocks or delaying their activation, and treating septic, cardiogenic, or hypovolaemic shock. The other line is dealing with the haemodynamic changes that lead to hypotension by referring to the haemodynamic pyramid (Fig. 1) and the pressure–output–resistance triangle (Fig. 2). This approach includes the following treatments, depending on patient status: treat bradycardia, treat arrhythmia, increase preload, enhance myocardial contractility, increase vasomotor tone, and increase blood viscosity. The status of intravascular volume and preload can be assessed using dynamic indices, such as pulse pressure variation and stroke volume variation. However, performance of these dynamic indices may vary during hypotension or normotension, which deserves further investigation.

Conclusions

Hypotension has heterogenous underlying pathophysiological mechanisms and effects on organ perfusion and patient outcomes in acute care. Hypotension does not always lead to organ hypoperfusion; in fact, it may not affect or may even increase organ perfusion, depending on the relative changes between the perfusion pressure and the RVR and pressure autoregulation. Available outcome evidence should be interpreted recognising their various biases and limitations. Overall RCT evidence does not support the notion that a higher BP target always leads to improved outcomes. Management of hypotension follows the diagnosis–decision-making–intervention axis, and it is challenging to define hypotension using one threshold for different patient populations under different clinical situations. When dealing with hypotension, it is essential to consider how well the BP is driving organ perfusion rather than focusing on a fixed BP value. To treat or not to treat hypotension is a complicated decision-making process that needs to take into account the patient's baseline condition, effects on organ perfusion, outcome evidence, and the nature of the procedure. Treatment follows two approaches: treating the direct causes or correcting the underlying haemodynamic changes responsible for the hypotension. These two approaches may sometimes overlap. Hence, the focus is on the heterogeneity of hypotension's underlying pathophysiology, effects on organ perfusion and patient outcomes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.06.048.

Declarations of interest

LM receives lecture fees from Edwards Lifesciences.

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Handling editor: Hugh C Hemmings Jr